CASE REPORT

Primary pleural epithelioid hemangioendothelioma (EHE) – two cases and review of the literature

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Abstract

Introduction: We present two cases with symptoms of progressively worsening cough, dyspnea, decreased exercise tolerance and right-sided back pain in the first case and upper respiratory symptoms characterized by cough and a low grade fever in the second case.

Methods: Report of two cases.

Results: The initial chest X-ray in both the cases showed pleural effusion. Further imaging with computed tomography of the chest confirmed the effusion in both cases. Thoracentesis was done in both of them revealed an exudative effusion that did not reveal any infection or malignancy. Both cases underwent surgical biopsy and the diagnosis of primary pleural epithelioid hemangioendothelioma was made.

Conclusions: Both the cases had progressive clinical deterioration despite chemotherapy with Taxol and Bevacizumab in one case and carboplatin, etoposide, and bevacizumab, in the second case. Both developed metastatic disease to lungs and died.

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Key words
epithelioid hemangioendothelioma – computed tomography – pleural effusion

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Authorship
We certify that all individuals who qualify as authors have been listed; each has participated in the conception and design of this work, the analysis of data (when applicable), the writing of the document, and the approval of the submission of this version.

Ethics
The case report and review of the literature was approved by the Institutional Review Board at the National Naval Medical Center for submission to publication. This is not a prospective study with patient enrollment. The clinical data, radiographic and pathology images do not disclose the identity of the subjects under the study.

Conflict of interest
None of the authors have any financial or personal conflicts in submitting this article.
The patients were seen the National Naval Medical Center, Bethesda, MD and all the physicians were involved in taking care of either one or both of the patients.
The work (evaluation and management of the two cases) was done at the National Naval Medical Center, Bethesda, Maryland.
All information regarding patient identifications are removed.
The views expressed in this article are those of the author and do not necessarily reflect the official policy or position of the Department of the Navy, Army, Department of Defense, nor the United States Government.

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14. ABSTRACT

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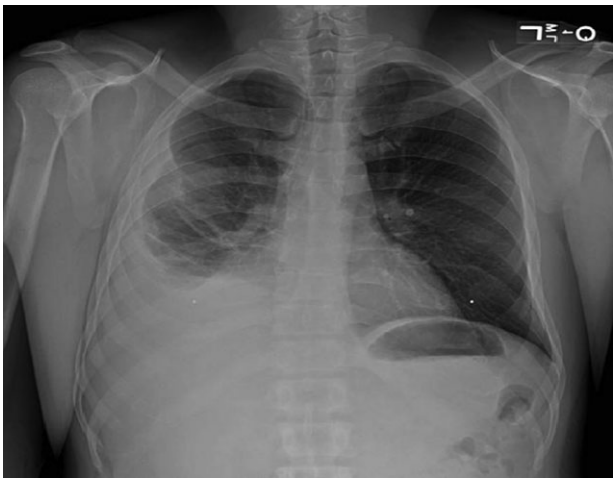

Figure 1. Chest X-ray showed elevated right diaphragm, with a meniscus and a right upper lobe (RUL) mass.

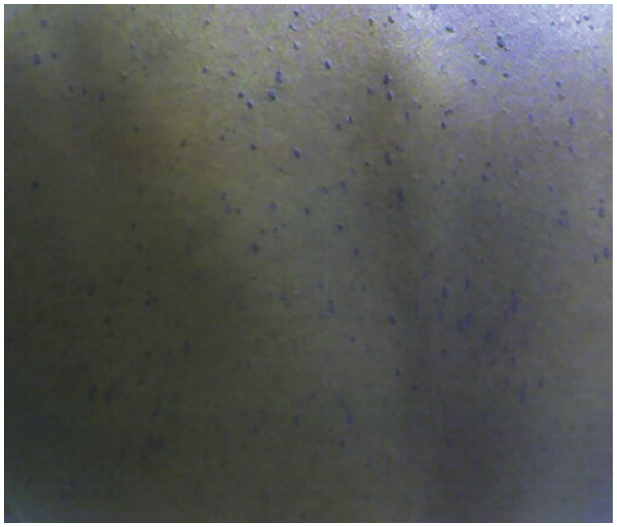

Figure 3. Hyperpigmented lesions (sign of Lesser Trelat).

Cases

Case 1

Forty two-year-old, non-smoking male presented with progressively worsening symptoms of cough, dyspnea, decreased exercise tolerance and right-sided back pain of 4 weeks' duration. He had no fevers, night sweats or weight loss. His chest radiograph showed a right upper lobe mass and right-sided pleural effusion (Fig. 1). Computed tomography (CT) of the chest with intravenous contrast demonstrated a right pleural effusion with fluid in the major fissure associated with a pseudotumor (Fig. 2). Initial evaluation included two CT guided fine needle aspirations of the mass that showed atypical inflammatory cells. The patient's past medical history included esophageal strictures requiring balloon dilation, hypertension and childhood asthma. His only medication was hydrochlorathiazide. He had a negative PPD test. On physical exam the patient was afebrile, normotensive and oxygen saturation was 99% on room air. He had decreased breath sounds on the right side of his chest and numerous raised deeply pigmented lesions with a 'stuck-on appearance' on his back that had appeared over the last couple of months (Fig. 3).

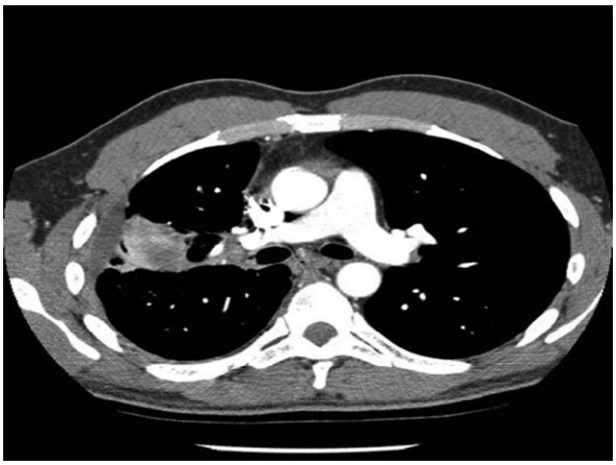

Figure 2. Computed tomography scan of chest showed right effusion and a pseudotumor in the major fissure.

Patient underwent thoracentesis with removal of 1.2 L of serosanguinous fluid that was exudative with a negative gram stain and cytology. The pleural fluid cell count demonstrated 13 000 red blood cells/uL (per cubic millimeter), 560 white blood cells/uL, 61 lymphocytes/uL, and the adenosine deaminase level was normal. On bronchoscopy, extrinsic compression of the right upper lobe bronchus with normal appearing mucosa was noted. Reaccumulation of pleural fluid was noted. Pleural fluid characteristics at the time of the second thoracentesis were similar to the first, and pleural pressures were not measured. The patient underwent video assisted thoracoscopy (VATS). At VATS, extensive pleural peel from the apex to the diaphragm was seen and required an almost complete pleurectomy. Pathologic review of the pleura demonstrated an intravascular bronchoalveolar tumor [also known as pulmonary epithelioid hemangioendothelioma (EHE)]. The patient was referred to Oncology where he was started on a regimen of Taxol and Bevacizumab. Computed tomography after completion of two cycles of chemotherapy demonstrated progression

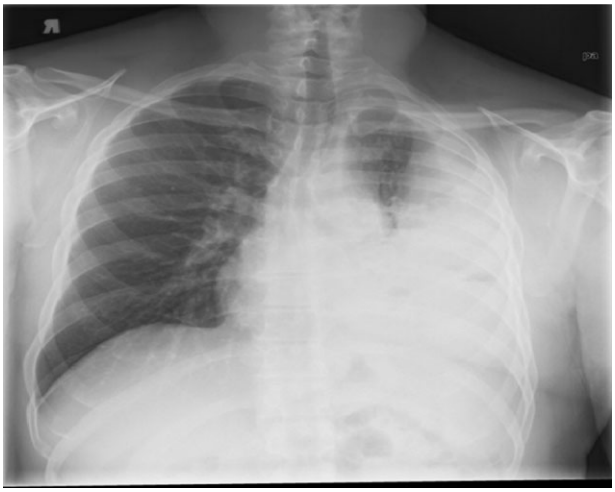

Figure 4. Left side effusion.

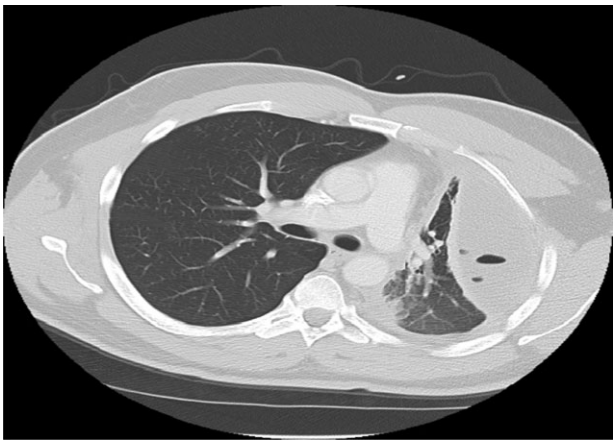

Figure 5. Left side loculated effusion.

of disease with the development of pulmonary nodules. The patient developed progressive right-sided pain, and acute renal failure, and died of cardiac arrest 8 months after his initial symptoms.

Case 2

Forty two-year-old African American male presented initially to his primary care physician with upper respiratory symptoms characterized by cough and a low grade fever. Chest X-ray demonstrated a small pleural effusion on the left and the patient was treated with oral antibiotics for presumed community acquired pneumonia. His past history includes type 2 diabetes mellitus and 15 pack-years of smoking. He worked as a licensed practical nurse at a county jail for the past 5 years and his yearly purified protein derivatives (PPDs) had been negative. He had no known asbestos exposure. He failed to improve on antibiotics and 3 weeks after initial presentation he developed progressive dyspnea. Follow-up chest radiography (CXR) demonstrated a large pleural effusion on the left (Fig. 4). CT of the chest, abdomen, and pelvis at that time did not reveal any other abnormalities (Fig. 5). Two thoracenetses were performed resulting in improvement of his dyspnea, but rapid fluid reaccumulation occurred. Diagnostic studies from both of the thoracenteses were consistent with exudative effusions, but were otherwise unremarkable with negative cultures (including AFB), cytology and normal ADA levels. A left thoracotomy was performed and the patient was found to have a fibrothorax. Decortication and biopsy were performed, and the pathology revealed large, atypical epithelioid cells immunoreactive with CD31 and CD34 within the parietal pleura (Figs. 6, 7). The diagnosis of malignant parietal EHE was made. Follow up CT scan 4 weeks later demonstrated diffuse parietal pleural thickening on the left, and multiple bilateral pulmonary nodules not previously observed. Metastatic disease was presumed after empiric therapy for septic emboli showed no improvement. The patient's disease progressed despite three cycles of carboplatin, etoposide, and bevacizumab, and he expired 6 months after his initial presentation.

Discussion

Intravascular bronchoalveolar tumor, also known as pulmonary EHE, is an uncommon vascular tumor with an intermediate malignant potential. EHE typically occurs in the liver, lung, bone or soft tissue. EHE was first described in 1975 by Dail and Liebow and was called 'intravascular bronchioloalveolar tumor' (1, 2).

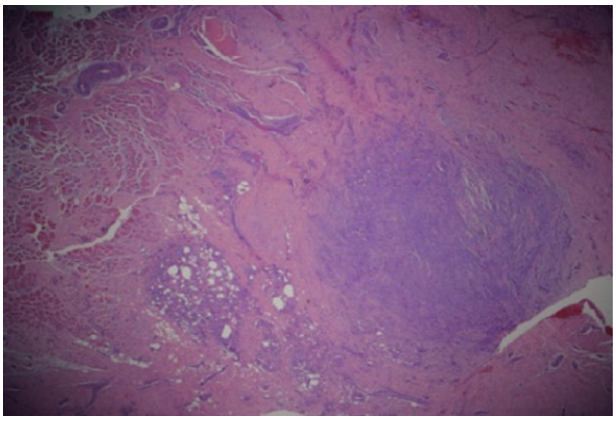

Figure 6. Tumor cells in low power.

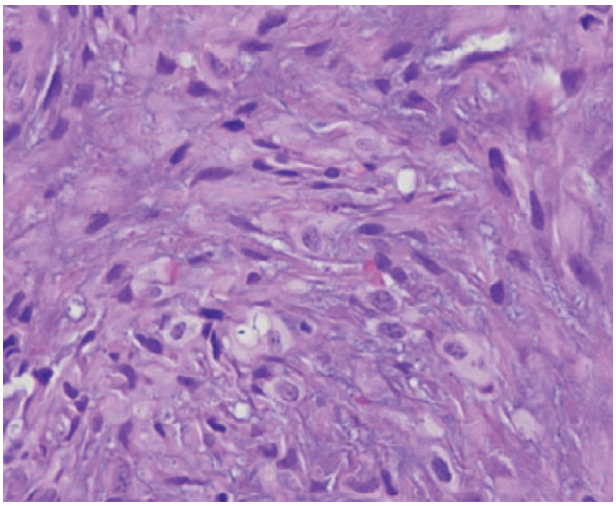

Figure 7. Tumor cells in high power.

In 1982, Weiss and Enzinger named the tumor as EHE (3). Primary sites of intrathoracic EHE most often include lung or the pleura, though less often mediastinal, rib and intracostal lymph nodes may be the site of a primary tumor (4–7). Histologically, this tumor is characterized by epithelioid or histiocytoid cell and can be distinguished from hemangiomas and sarcomas. Plasmacytoid cells with cytoplasmic vacuoles and multinucleation are seen. Immunohistochemical stains reveal CD31, CD-34, factor VIII and vimentin-positive neoplastic cells (2, 3, 8). The pulmonary EHE is often seen as bilateral nodules with a female predominance and age ranging from 12 to 60 years. Nearly 50% of the cases are seen in patients less than 40 years of age (9). Risk factors are not well established. Although asbestos exposure has been considered, Attanoos *et al.* noted no definite association between pleural EHE and asbestos exposure. Small numbers limit the data however, as only three cases of EHE were reported compared with 92 cases of mesothelioma (10). Kitaichi reported 3 out of 21 cases that had spontaneous regression at 5, 13 and 15 years after initial diagnosis (11). Patients may be asymptomatic and the tumors are recognized on routine chest radiograph. On computed tomography pulmonary EHE typically presents as multiple perivascular nodules with margins that may or may not be well-defined. Other less common findings include ground glass opacities, interlobular septal thickening, and pleural effusion (11, 12). Dail *et al.* reported 25% of patients with more than 20 nodules. These pulmonary nodules are often slow growing and can be treated surgically. Patients with parenchymal disease usually have a good prognosis and a life expectancy of 15–20 years (2, 12–15). The predictors for poor survival in patients with parenchymal disease include clinical symptoms such as cough, hemoptysis, chest pain. Additionally, an associated pleural effusion and metastatic disease portend a poor prognosis (12–16). Primary pleural EHE is rare but has an aggressive course with a very poor prognosis. Crotty *et al.* reported four cases of pleural EHE and all were symptomatic with chest pain and dyspnea at the time of presentation. All four of these patients had right-sided pleural EHE with small to moderate size pleural effusion on chest with volume loss on chest radiography, and no evidence of mediastinal adnopathy or bone abnormalities in the thorax. On computed tomography, smooth and nodular thickening of the pleura with mediastinal invasion was noted and one had mediastinal node enlargement. The pleural thickening was diffuse in two and confined to lower chest cavity in two patients. Two patients had multiple metastatic pulmonary nodules (17). Although pulmonary EHE is most commonly seen in women with a fairly good prognosis, pleural EHE often seen in men and has a poor prognosis. Pleural EHE at presentation is often advanced, and curative resection is often not possible (17–19). Adjunctive chemotherapeutic regimens have been used with agents such as carboplatin, etoposide, and bevacizumab. The rationale for bevacizumab relates to multiple reports of VEGF-R expression on EHE cells. However, the benefits of chemotherapy are not known, and life expectancy can vary from 1 to 2 years. Pinet *et al.* reported complete response to Carboplatin and Etopiside in one patient (20). EHE arising from the innominate vein and brachiocephalic vein presenting as an anterior mediastinal mass have been reported. Histological mediastinal EHE would be differentiated from metastatic adenocarcinoma and sarcomas. The clinical course of mediastinal EHE varies from no recurrence following surgery and chemotherapy to recurrence (4–6).

The appearance of deeply pigmented raised lesions on the back of our first patient back in the months preceding the initial onset of symptoms most likely represents the sign of Lesser Trelat. The sign of Lesser Trelat is a paraneoplastic syndrome of unknown etiology that is marked by the sudden eruption of seborrhoeic keratosis in young patients. Multiple tumor types are associated with the sign of Lesser Trelat, though to our knowledge this is the first case of EHE associated with this sign reported in the literature.

In summary, EHE is a rare tumor and can arise from the pulmonary parenchyma, pleura, mediastinum or the rib. The pleural EHE is a progressive disease and patients die of respiratory compromise.

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